ABSTRACT

Studies of tryptophan (Trp) metabolism in relation to the serotonin status in alcoholism are of 2 types: (1) those related to the pharmacological effects of ethanol; (2) those concerning the serotonin status in the absence of alcohol intake. In experimental animals, acute and chronic ethanol administration and subsequent withdrawal exert a variety of effects on brain serotonin synthesis and turnover mediated by corresponding changes in Trp availability to the brain secondarily mainly to modulation of liver Trp pyrrolase (TP) activity. Alcohol-preferring mice and rats exhibit a central serotonin deficiency caused by, or in some cases associated with, a higher TP activity. Liver TP also appears to be a target of ethanol in man and evidence has recently emerged that alcoholics with positive family history are serotonin-deficient because of a lower availability of circulating Trp to the brain. Acutely, ethanol depletes brain serotonin in normal subjects, which may explain alcohol-induced aggression in susceptible individuals and also the incidence of depression in alcoholism. Trp availability to the brain is increased before the appearance of the alcohol-withdrawal syndrome in man, raising the possibility that the associated behavioural disturbances may involve the excitotoxic Trp metabolite quinolinate. Further studies of the Trp and serotonin status in relation to these important clinical features of alcohol dependence and alcoholism may therefore yield fruitful results.

1. INTRODUCTION

Tryptophan (Trp) is the most extensively studied amino acid in relation to alcohol and alcoholism, because it is the precursor of the indolylamine 5-HT (5-hydroxytryptamine or serotonin). Initially, interest in 5-HT in relation to alcoholism centred on its role in the regulation of mood, disturbances of which are important clini-
ical features of alcohol dependence and the alcohol withdrawal states. However, although this particular interest continues, emphasis has shifted for over a decade now to the role of 5-HT in the control of alcohol consumption itself (for reviews, see Naranjo et al., 1986; Sellers et al., 1992). Many more studies of Trp and 5-HT metabolism in relation to alcohol and alcoholism have been performed in experimental animals, in comparison with man, but, as will be seen below, many of the effects of ethanol in animals may also occur in man. Brief (Badawy, 1988, 1996) and more detailed (LeMarquand et al., 1994a,b) accounts of the effects of ethanol on Trp and 5-HT metabolism have been published. In reviewing these effects, description will be concerned mainly with serotonin metabolic changes as related to altered Trp disposition. For alterations in other aspects of serotonin function (e.g. receptor physiology), the reader should consult the reviews by LeMarquand et al. (1994a,b).

Studies in experimental animals have in general led to conflicting results, largely due to differences in a variety of experimental conditions, such as the animal species and strains tested, the nutritional status of the animals used, doses of ethanol and routes of its administration, and methods of assessment of some of the parameters measured, e.g. 5-HT turnover rate. Despite such differences, the most important determinant of the effects of ethanol on Trp and 5-HT metabolism is the condition of ethanol administration under which studies have been performed, i.e. whether ethanol was administered to animals acutely or chronically. In the former case, the time interval after acute administration may be a critical factor, as will be shown below, whereas, in the latter case, a major determinant of the ethanol effect is whether studies are performed under chronic conditions, or during subsequent withdrawal. The same principles apply to a large extent also to human studies.

2. STUDIES IN EXPERIMENTAL ANIMALS

2.1. Pharmacological Effects of Ethanol

2.1.1. Acute Effects. In the most extensively studied animal species, the rat, whose Trp metabolism and disposition resemble most closely those of man, acute ethanol administration exerts a biphasic effect on brain serotonin synthesis and turnover; an initial enhancement followed by a later inhibition (Badawy and Evans, 1976). The initial enhancement is caused by an increase in circulating free (ultrafiltrable) Trp availability to the brain secondarily to a catecholamine-dependent lipolysis and, hence, non-esterified fatty acid (NEFA)-mediated displacement of the albumin-bound amino acid, whereas the later inhibition of 5-HT synthesis and turnover is the result of a decrease in circulating Trp (free and albumin-bound) availability to the brain secondarily to activation of liver Trp pyrrolase (Trp 2,3-dioxygenase, EC 1.13.11.11, TP) by the earlier increase in free Trp availability (to the liver). It should be noted here that this activation of liver TP by acute ethanol administration, which is substrate (Trp)-mediated (see Badawy and Evans, 1973, 1975a, 1976), occurs in rats studied in the fed state. In rats starved for 24h, activation of liver TP by acute ethanol administration is caused by a cofactor (haem)-mediated mechanism (C. J. Morgan and A. A.-B. Badawy, unpublished work) (for differences between these and also the hormonal mechanism, see Badawy and Evans, 1975b); the above difference will be discussed further below in relation to the acute effects of ethanol in fasting normal human subjects.

It is noteworthy that in none of 11 studies of the acute effects of ethanol on liver TP activity was there any suggestion of inhibition, and that the controversial findings in